The Egyptian Heart Journal (2012) **64**, 15–20

Egyptian Society of Cardiology

The Egyptian Heart Journal

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ORIGINAL ARTICLE

Short term statin treatment in idiopathic dilated cardiomyopathy

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Received 20 December 2010; accepted 16 February 2011
Available online 29 December 2011

KEYWORDS

Statins;
Cardiomyopathy;
CRP

Abstract *Background:* Statins may provide additional benefits in patients with cardiac failure due to their pleiotropic effects besides their cholesterol-lowering actions. In this study, we aimed to evaluate the impact of 12-week 40 mg atorvastatin therapy on the inflammatory markers, endothelium dependent vasodilatation and the ventricular performance markers in patients with heart failure (HF).
Methods and results: Thirty chronic symptomatic heart failure patients, all with idiopathic dilated cardiomyopathy (DCM) were included to this open label and prospective study. Thirty patients were subdivided into two groups: group I – 15 patients who were given 40 mg of atorvastatin and group II – 15 patients who were given a placebo. After a 12-week treatment with atorvastatin 40 mg/day; clinical functional capacity, echocardiographic indices of cardiac performance and inflammatory markers were evaluated. After the treatment, even though the left ventricular ejection fraction (LV EF) did not improve significantly in the group receiving statins (29.2 ± 6.18 to 29.73 ± 6.27 in the statin group and 28.13 ± 5.81 to 27.93 ± 5.56 in the control group), both the 6 min walk test and Minnesota living with heart failure questionnaire improved significantly ($p = 0.000$ and 0.022, respectively). The flow mediated dilatation in the brachial arteries also showed improvement in the statin receiving group (8.9–13.8 in the statin group $p = 0.0001$, and 9.5–10.2 in the control group $p = 0.055$). In addition, the statin receiving group showed significantly lower levels of highly sensitive C-reactive protein

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Peer review under responsibility of Egyptian Society of Cardiology.
doi:10.1016/j.ehj.2011.08.020

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(hs-CRP) levels at follow up (4.6–1.93 in statin group $p = 0.005$, and 7.2–4.97 in the control group $p = 0.176$).

Conclusion: Short term atorvastatin treatment improved functional capacity and the clinical symptoms in HF patients with idiopathic dilated cardiomyopathy. This positive effect of atorvastatin might be secondary to inflammatory modulation and improvement of endothelial function. Statins in HF deserve special attention by means of further large-scale trials.

1. Introduction

The 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, or statins are drugs that were originally designed to lower high levels of plasma cholesterol in hyperlipidemic patients, and were found to improve endothelial functions and decrease plasma concentrations of tumor necrosis factor (TNF) in patients with coronary artery disease and hyperlipidemia. Statins have also been shown to reduce morbidity and mortality in those patients.[1]

However there is increasing evidence of benefit in using statins to treat patients with normal cholesterol level and non-ischemic heart failure. In such patients statins treatment improves endothelial functions and neurohormonal imbalance as shown in the experimental and clinical studies.[2]

Statins may retard the progression of chronic heart failure, not only through effects that may directly impact coronary ischemia, namely restoration of endothelial function and plaque stabilization, but also by additional properties such as effects on myocardial function, down-regulation of AT-1 receptors, and inhibition of pro-inflammatory cytokines.[3]

As statins improve peripheral and coronary endothelial functions through low density lipoproteins lowering and pleiotropic mechanisms, treatment with statins would improve hemodynamic abnormalities in patients with cardiac failure even in the absence of underlying coronary artery disease.[4] Accordingly we were aiming to study the effects of short term atorvastatin therapy on functional capacity, clinical symptoms, endothelial functions and cardiac function in patients with normo-cholesterolemic idiopathic dilated cardiomyopathy in a placebo-controlled study.

2. Patients and methods

The study was conducted on 30 patients presenting with chronic symptomatic heart failure, diagnosed to have idiopathic dilated cardiomyopathy (DCM) who were recruited from the Cardiology Department at the outpatient clinic at the Ain Shams University Hospital during their follow up visits. All patients were receiving standard anti-failure treatment in the form of loop diuretics, B-blockers plus an angiotensin converting enzyme inhibitor or angiotensin II receptor blocker with or without digoxin and spironolactone in unchanged dose for at least one month before the study. The patients were divided into two groups: group I – 15 patients who were maintained on atorvastatin 40 mg for 3 months in addition to their full anti-failure treatment and group II – 15 patients who were maintained on placebo for the same period of three months besides their full anti-failure treatment.

Inclusion criteria were:

1. Non-ischemic heart failure, with an LV ejection fraction of $< 40\%$.
2. Normal lipoprotein pattern.
3. Symptomatic heart failure (HF), New York Heart Association (NYHA) functional class II or III.
4. Anti-failure drugs fixed for 1 month before the study.

While exclusion criteria were:

1. Presence of ischemic heart disease.
2. Any renal, hepatic or pulmonary vascular dysfunction.
3. Valvular heart disease.

All patients were subjected to the following:

1. History taking.
2. Clinical examination.
3. Assessment of quality of life for all patients guided by Minnesota living with a heart failure questionnaire (MLHFQ).[5]:

This questionnaire was designed to measure the effects of heart failure and treatments of heart failure on an individual quality of life.[6] It is also used to measure the effect of symptoms, functional limitations and psychological distress on an individual's quality of life. The MLHF questionnaire asks each person to indicate using a six point, zero to five, Likert scale as to how much each of the 21 facets prevented them from living as they desired by marking either 0, 1, 2, 3, 4 or 5 to indicate how much the selected symptom, functional limitation or psychological distress affected the patient's life during the past month where zero (0) means not at all, one (1) means very little and five (5) very much.

4. Assessment of highly sensitive C-reactive protein (hs-CRP) as laboratory markers of endothelial functions.

Samples for hs-CRP were analyzed in the local laboratory. Samples were analyzed within 24 h using the Synchron LX 20 system CRPH reagent (Beckman Coulter, High Wycombe, UK) assay.[7]

5. The 6 min walk test (6MWT).

The 6MWT is a useful measure of functional capacity targeted at people with mild or moderate impairment. It has been widely used for measuring the response to therapeutic interventions for pulmonary and cardiac diseases. The new American Thoracic Society guidelines provide a standardized

Table 1 Demographic data distribution in both groups.

		Age Mean ± SD	Gender	
			Males	Females
Study population	Group I	50.600 ± 11.128	8	7
	Group II	45.600 ± 7.726	8	7
T-test	*t*	−0.359	−3.334	
	p-Value	0.722 (NS)	0.872 (NS)	

Table 2 Risk factors distribution in both groups.

	HTN	DM	Smoking
Group I	6	6	6
Group II	1	3	6
p-Value	0.000	0.292 (NS)	0.977 (NS)

approach for performing the test. Absolute contraindications for the 6MWT include the following: unstable angina during the previous month and myocardial infarction during the previous month. Relative contraindications include a resting heart rate of more than 120, a systolic blood pressure of more than 180 mm Hg, and a diastolic blood pressure of more than 100 mm Hg.[8] The 6MWT was performed indoors, along a flat, straight, enclosed corridor with a hard surface that is seldom raveled. If the weather was comfortable, the test may be performed outdoors.

6. Brachial ultrasound.

Conduit artery function was assessed by brachial ultrasound based on the protocol described by Celermajer et al.[9] The assessment adhered to guidelines published by the International Brachial Reactivity Task Force and used a fully digitalized ultrasound system (GE Medical Systems) with a high-resolution, broad-spectrum transducer.[10] The brachial artery was imaged in the longitudinal plane during the baseline resting phase, after 5 min of forearm ischemia to assess endothelium-dependent flow-mediated dilatation (FMD) and after sublingual nitrates that were given to assess endothelium-independent dilatation (EID).

7. Transthoracic echocardiography.

Transthoracic echocardiographic examinations were performed using a General electric echocardiogram VIVID 5. The examination was conducted with participants in the left lateral position. M, mode echocardiographic variables were measured according to the recommendations of the American Society of Echocardiography.[1,11] Left ventricular ejection fraction was calculated.

2.1. Statistical analysis

All the data were gathered, tabulated, and statistically analyzed on a PC computer using the commercially available statistical software package SPSS 12. The following tests were done:

1. Mean standard deviation (SD).
2. T test and Wilcoxon signed-rank test for independent samples.
3. Chi square test (χ^2).
4. ANOVA test.

Data are presented as mean ± SD with 95% CI. $p < 0.05$ was considered significant.

3. Results

All patients were age and sex matched (Table 1). Risk factors distribution are shown in (Table 2).

Use of statins in the current study was associated by significant improvement of the functional capacity as assessed by 6MWT ($p < 0.05$) (Table 3), MLHF questionnaire ($p = 0.022$) (Table 4) and NYHA functional class (Tables 5 and 6).

In statins-treated patients, there was a significant reduction of hs-CRP ($p = 0.005$) (Table 7) in addition to significant improvement of endothelial functions as assessed by improvement of FMD measured by brachial ultrasound (Table 8).

However, use of statins was not associated with a statistically significant improvement of LVEF as assessed by echocardiography (Fig. 1).

4. Discussion

The benefits of statins in heart failure are supported by experimental and clinical studies. Statins were originally designed to lower plasma cholesterol. However, the idea that statins mediate effects beyond cholesterol lowering, namely through the so-called pleiotropic effects, is gaining increased strength.[12]

Furthermore, evidence in favor of the therapeutic benefits of statin treatment in patients with non-ischemic heart failure, irrespective of serum cholesterol values or atherosclerotic disease, has been recently provided by several authors.[13]

We studied the effects of statins versus placebo in 30 patients suffering from dilated cardiomyopathy. This was done through several parameters including assessment of the functional capacity of the patients included in the study using 6MWT and MLHFQ scoring before and after the use of statins and placebo in both groups. Measurement of hs-CRP was done for all patients included in the study as a marker of endothelial functions and to detect any improvement of endothelial inflammation found in patients with CHF.

Brachial ultrasound was done for the assessment of improvement in the functions of the endothelial tissues through measurement of FMD and EID before and after the use of statins and placebo. Finally assessment of systolic func-

Table 3 6MWT in both groups.

6MWT	Before	After	Paired T-test	
	Mean ± SD	Mean ± SD	*t*	*p*-Value
Study population				
Statins	287.271 ± 44.401	333.579 ± 36.361	−7.579	0.000*
Placebo	274.040 ± 50.120	278.087 ± 52.443	−1.600	0.132 (NS)

Table 4 The MLHFQ scoring in both groups.

MLHFQ scoring	Before	After	Paired T-test	
	Mean ± SD	Mean ± SD	*t*	*p*-Value
Study population				
Statins	33.667 ± 8.964	31.267 ± 7.934	2.581	0.022*
Placebo	26.000 ± 6.568	26.133 ± 7.019	−0.323	0.751 (NS)

Table 5 NYHA functional class before the onset of treatment.

	NYHA class		Total
	II	III	
Statins			
N	7	8	15
%	46.67	53.33	100.00
Placebo			
N	5	10	15
%	33.33	66.67	100.00
Chi-square			
χ^2	3.467		
p-Value	0.325		

Table 6 NYHA functional class after administration of atorvastatin.

	NYHA class			Total
	I	II	III	
Statins				
N	2	11	2	15
%	13.33	73.33	13.33	100.00
Placebo				
N	1	6	8	15
%	6.67	40.00	53.33	100.00
Chi-square				
χ^2	16.059			
p-Value	0.013			

tions in patients with DCM was done using transthoracic echocardiography for measurement of LVEF before and after the use of drugs.

As regards the functional capacity of the patients and use of statins were associated with clinical improvements detected first by improvement in the meters walked in the 6MWT. In contrast, patients on placebo showed no significant change in meters walked in the 6MWT before and after the use of placebo. Also as regards MLHFQ scoring, patients who took statins for 3 months showed an improvement in the scoring scale. Improvement in MLHFQ scoring of more than or equal to 5 points was considered to be clinically meaningful and sufficient for majority of patients in one study to take a medication that had no side effect or costs.[14] In our study more than 50% of the patients who showed an improvement in MLHFQ scoring after treatment with statins gave an improvement of more than or equal five points. This was in contrast to patients on placebo who showed no significant change in MLHFQ scoring after 3 months of treatment.

The results of the current study as regards the improvement of 6MWT and MLHFQ scorings are concordant with those of Strey et al.[13] and in their study they demonstrate that the short term statin treatment improves endothelial function and neurohormonal imbalance in normo-cholesterolemic patients with non-ischemic heart failure with the resultant improvement of the clinical parameters of functional capacity of the patients namely the 6MWT and MLHFQ. Also the results of the current study are concordant with Laufs et al.[14] who randomized a small number of patients with non-ischemic dilated cardiomyopathy (NYHA classes II–III) to statins or placebo for an average treatment period of 20 weeks. They observed that sta-

Table 7 Showing hs-CRP levels at baseline and after 3 months of atorvastatin or with placebo.

hs-CRP	Before	After	Wilcoxon signed ranks test	
	Mean ± SD	Mean ± SD	*Z*	*p*-Value
Study population				
Statins	4.600 ± 3.470	1.926 ± 0.742	3.302	0.005*
Placebo	7.286 ± 5.841	4.974 ± 5.109	1.263	0.176 (NS)

Table 8 Baseline FMD and EID in both groups and follow up FMD and EID after 3 months of treatment (statins or placebo) in both groups.

Study population	Before	After	Paired T-test	
	Mean ± SD	Mean ± SD	*t*	*p*-Value
FMD				
Statins	8.933 ± 3.474	13.800 ± 3.550	−12.934	0.000*
Placebo	9.533 ± 4.868	10.200 ± 4.960	−2.092	0.055 (NS)
EID				
Statins	9.533 ± 3.543	9.600 ± 3.641	−0.564	0.582 (NS)
Placebo	10.200 ± 4.739	10.267 ± 4.713	−0.435	0.670 (NS)

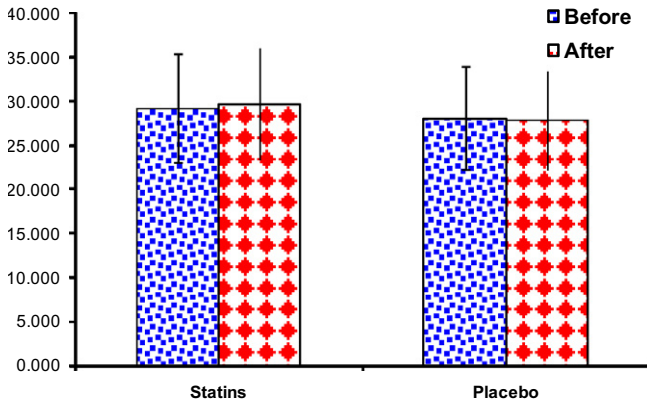

Figure 1 Base line LVEF and follow up after 3 months of treatment (statins or placebo).

tin treatment resulted in an improvement in the quality of life and exercise capacity of the patients.

Assessment of the functional capacity of all patients included in the study was also done using the New York Heart Association functional class (NYHA). The current study showed a significant decrease in the NYHA functional class in the statin-treated patients in both groups but not in patients taking placebo. The results of the current study are concordant with those of Wojnicz et al.[15] and in their study they demonstrate that the treatment with atorvastatin in addition to standard therapy for heart failure may significantly improve clinical outcomes leading to a significant improvement of NYHA functional class in this cohort of patients. Also the results are concordant with the results obtained by Node et al.[16] who demonstrated that patients with symptomatic non-ischemic dilated cardiomyopathy (NYHA classes II–III) who were randomized to statins for 14 weeks had an improvement in the NYHA functional class.

Inflammatory markers are increased in chronic heart failure (CHF), including high-sensitivity C-reactive protein (hs-CRP), which is produced in the liver in response to the cytokine interleukin-6 (IL-6).

Highly sensitive CRP as a marker of endothelial functions showed a significant reduction in its serum level when measured after 3 months of taking atorvastatin 40 mg. Patients on placebo showed no significant change in the serum levels of hs-CRP after 3 months of treatment. The results of the current study are concordant with those of Sola et al.[17] and in their study they concluded that the use of atorvastatin in patients with non-ischemic heart failure improves the vascular markers of inflammation including hs-CRP, interleukin-6 (IL-6), and tumor necrosis factor-alpha receptor II (TNF-α RII). Also a study by Tousoulis et al.[18] gave similar results where they examined the use of low dose atorvastatin on the inflammatory markers and endothelial function in patients with heart failure, resultant improvement of endothelial function and significant reduction of inflammatory markers including hs-CRP. Another study by Horwich et al.[19] also gave rise to similar results regarding the improvement in the endothelial function and reduction of inflammatory biomarkers with statin therapy in patients with heart failure.

The results of the current study as regards the significant reduction of serum levels of hs-CRP were different from those of Bleske et al.[20] and in their study they found that the use of statins in patients with non-ischemic cardiomyopathy was associated by neutral effect on the inflammatory markers including hs-CRP, tumor necrosis factor-alpha, intracellular adhesion molecule-1, and circulating levels of vascular adhesion molecule-1. The difference in the results of the current study from this study may be due to relatively small population study conducted by Bleske et al. where the effects of statins were studied on 15 patients with non-ischemic heart failure.

In the current study assessment of endothelial function was also done using brachial ultrasound for measurement of FMD and EID. FMD showed a significant improvement after 3 months of atorvastatin 40 mg therapy, while patients on placebo showed no improvement in FMD after 3 months of treatment. EID showed no significant change either with statin therapy or in those of placebo. The current study gave rise to results that are concordant with Strey et al.[13] in a study that investigate the effect of short term statin therapy on impaired endothelium-dependant vasodilatation typically occurring in chronic heart failure (CHF). After 6 weeks of placebo and atorvastatin 40 mg in patients with non-ischemic CHF the FMD was significantly improved after using statins but not in the placebo group whereas EID did not change in either group.

LVEF was measured according to the recommendations of the American Society of Echocardiography[1] where it showed no significant change either with placebo or with statin therapy in patients with DCM. The current study was different from Wojnicz et al.[15] in their study who found that there is a significant improvement (an increase of > 5%) in the absolute left ventricular ejection fraction in patients with DCM after using atorvastatin 40 mg for 6 months. Also the current study was different from a study by Yamada et al.[21] and Liu et al.[22] who both found that there is a significant increase in the LVEF in patients with chronic heart failure after using statins for a period of 31 ± 14 months. The difference in the results of the current study from these studies may be due to the relatively short duration of the study in comparison to the other studies.

5. Conclusion

Use of statins in normo-cholestrolemic patients with non-ischemic heart failure improves the functional capacity of such patients. Statin treatment when added to the standard antifailure measures in patients with CHF improves endothelial function and lowers serum levels of inflammatory biomarkers.

Recommendations

Further investigations and larger randomized studies should be undertaken to either confirm or exclude the benefit of statins in patients with normal lipid profile and non-ischemic heart failure.

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